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MOLECULAR DEVICES CORPORATION

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

CALIPER TECHNOLOGIES CORP., Plaintiff, v. MOLECULAR DEVICES CORPORATION, Defendant. AND RELATED COUNTERCLAIMS.	Case No. C 02-01837 JSW (JL) **MOLECULAR DEVICES' OPPOSITION TO MOTION FOR PRELIMINARY INJUNCTION** **[REDACTED]** **Date: May 16, 2003** **Time: 9:00 A.M.** **Ctrm: 2** **Judge: Honorable Jeffrey S. White**

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I. INTRODUCTION

Caliper Technologies Corp. ("Caliper") is not entitled to a preliminary injunction against Molecular Devices Corporation ("MDC") after delaying over a year to bring its motion, and because ***MDC does not use the fluorescence polarization assay method of the '774 and '141 patents in MDC's IMAP™ assay kits***. In fact, not even Caliper uses the patented method.

Caliper was well aware of MDC's IMAP™ technology in September 2001, and even obtained IMAP™ assay kits when they were released by MDC a few months later. Yet, Caliper waited months before filing suit, and many more months before bringing this motion.

By bringing this action, Caliper appears to be trying to prevent the use of the better assay (IMAP™) that runs on customers' existing equipment so that Caliper can sell its more expensive, highly specialized, but often slow and inconvenient equipment. There can be no other reason, for Caliper does not even sell assay kits using its own patented technique. Caliper's motion for preliminary injunction should be denied.

II. SUMMARY OF ARGUMENT

The preliminary injunction motion should be denied because:

- Caliper's '774 and '141 patent claims are invalid as they are anticipated by the Seethala publication, and are unenforceable for failure to disclose material prior art (Seethala) to the U.S. Patent and Trademark Office.
- Caliper cannot establish irreparable harm; where it delayed bringing the instant injunction motion over a year after it knew of MDC's IMAP™ technology, and obtained MDC's IMAP™ assay kits; and where Caliper's failure to sell customers on its new high-throughput screening, "systems" has less to do with IMAP™, and more to do with the fact that Caliper's system doesn't work well, doesn't measure fluorescence polarization, and is a departure from industry standards.
- Further, the harm to MDC's business reputation, customer relationships and vendor contracts should an injunction issue, far outweighs any hardship Caliper would experience while waiting for a remedy after a verdict in this case.
- Public policy also favors continuing drug research without interruption.

III. STATEMENT OF FACTS

A. Kinase Enzyme Research

The MDC IMAP™ assay kits at issue in this case are designed to detect and measure the activity of an enzyme, particularly a kinase enzyme, using an old technique called fluorescence polarization. Kinases are enzymes that occur naturally in the body and are essential for the normal function of cells. Abnormal kinase activity has been linked to various cancers, auto-immune diseases, inflammatory diseases (such as asthma), diabetes, neurological disorders and cardiovascular (heart) diseases. (See Declaration of J. Richard Sportsman ("Sportsman Decl.") ¶ 12.) Thus, there is considerable interest in finding drugs that "inhibit" kinase activity ("kinase inhibitors"), which could be used to control these diseases.

Although there are many different kinases in the body, ***each kinase does one simple thing – it transfers a phosphate from one molecule to another.***[6] Detecting whether that transfer of phosphate takes place is what IMAP™ and other kinase assays are all about. If the kinase inhibitor drug being tested has no effect on the kinase (the drug doesn't work), the phosphate will be transferred by the kinase (the kinase did work). If the drug being tested works to inhibit the kinase, the phosphate will not be transferred by the kinase. (Sportsman Decl. ¶¶ 13, 14 and 44.) This process of the kinase transferring a phosphate from one molecule to another is called "phosphorylation". If the assay results in a "phosphorylated" product, it means the kinase did its job and was not inhibited – that is, the drug didn't work. *Id.* In drug research, the kinase usually works because finding an inhibiting drug is like finding the needle in the haystack.

B. Fluorescence Polarization Is An Old Technique.

Fluorescence polarization is a detection technique that has been known since the 1920's when scientists first developed the techniques to measure and analyze it. (Sportsman Decl. ¶ 11.) Fluorescence is similar to what makes glow-in-the-dark toys and posters visible after you shine light on them. Things that fluoresce emit light shortly after being "hit" with light. Scientists can attach a molecule that emits fluorescent light – known as a fluorescent "tag" or "label" – to a molecule that does not emit fluorescent light, and which would otherwise be invisible. Scientists can then detect the otherwise invisible molecule by the fluorescent "glow" of the tag that was attached to it. (Sportsman Decl. ¶ 7.)[7]

Fluorescence polarization measures the "polarization" of the light emitted by the fluorescently labeled tag on the molecule (polarization is essentially light emitted along one direction or plane). (Sportsman Decl. ¶ 8.) Small fluorescently tagged molecules tumble and spin quickly emitting light in many random directions. The net result is "low fluorescence polarization". Conversely, large, slow moving fluorescently tagged molecules tend to emit light in one plane or direction – this is "high fluorescence polarization". (Sportsman Decl. ¶¶ 7-11.) Accordingly, the

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[6] Phosphate is labeled as PO_4 because it has one phosphorous atom and four oxygen atoms. (Sportsman Decl. ¶ 13.)

[7] A fluorescently tagged molecule can be analogized to a small glow-in-the-dark sticker affixed to a golf ball in a dark room. You could not see the golf ball, but you could see the sticker attached to it.

fluorescence polarization of molecules can be used to determine whether there are large or small fluorescent molecules in the sample or mixture. (Sportsman Decl. ¶ 9.) Small fluorescent molecules will have low fluorescence polarization because they spin and tumble quickly, while large, slow molecules will have high fluorescence polarization.

Fluorescence polarization has also been used to determine whether a small fluorescently tagged molecule is bound to a bigger molecule. When the small molecule is bound to a large molecule, it "acts and looks" like a large molecule. That is, it tumbles slowly and has high fluorescence polarization. (Sportsman Decl. ¶ 10.) If the small molecule does not bind to the large one, it acts and looks like the small molecule, that is, tumbling fast and having a low fluorescence polarization. Thus, measuring the fluorescence polarization is one way to determine whether the small molecule is of a kind that could bind to a particular large one. Low fluorescence polarization indicates that the small molecule did not bind with a big one, while high fluorescence polarization indicates that the small molecule did bind to the large one.[8]

C. The Prior Art Fluorescence Polarization Kinase Assay

Like the earlier fluorescence polarization methods, the Caliper method in the '774 and '141 patents is used to see if a kinase was able to transform a "starting material" into what is called the "reaction product", by transferring a phosphate group to the reaction product. (Miclean Decl. Ex. P;

[8] Binding a fluorescently tagged small molecule to a large molecule can be analogized to attaching the golf ball with its glow-in-the-dark sticker, to a large, heavy medicine ball, which would dramatically slow down the movement of the golf ball (if the golf ball were spinning).

Nikiforov Tr. 265:20-266:6; 140:5-18; 140:23-142:18; 271:15-24; Barron Decl. ¶ 6). The starting material has two important features: (1) it has a fluorescent label or tag attached to it, which will allow scientists to track what happens to it, and (2) it as the ability to have a phosphate group added to it by the kinase.[9] In the both the Caliper and the earlier fluorescence polarization methods, this fluorescently tagged starting material is placed into a mixture containing water, among other things.[10] Then, ATP[11] and the kinase (which has been incubated with the potentially inhibitory drug) are added to that mixture.[12] If the kinase works (and is not inhibited), it will transfer a phosphate group from ATP to the fluorescently-labeled starting material, creating the fluorescently tagged reaction product – a "phosphorylated" version of the starting material.[13] (Miclean Decl. Ex. P; Nikiforov Tr. 26:12-15; 43:7-25; 93:20-94:3; 265; 271:21-272:10; 272:15-21; Barron Decl. Ex. C.)

Yet, regardless whether the kinase worked to transfer a phosphate to the starting material – thus creating the reaction product – both the fluorescently tagged starting material and reaction product would be small molecules that spin fast and tumble – emitting their light in many directions (low fluorescence polarization.) This would make them indistinguishable. To detect and distinguish the reaction product (to determine if the kinase worked) scientists had to make it act like a big and slow molecule so it could emit light in one direction (high fluorescence polarization.) (Sportsman Decl. ¶ 8-10.)

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[9] In the words of claim 1 of the '774 patent, this is a "first reagent having a fluorescent label"; In the words of claim 1 of the '141 patent, this is a "phosphorylatable compound that includes a fluorescent label". "Phosphorylatable" simply means that a phosphate group can be chemically added to the molecule by the action of the kinase; that transferring of the phosphate by the kinase is called "phosphorylation", and the product of that reaction is a "phosphorylated" product. (Miclean Decl. Ex. MM, Col. 29, l. 1-25; Ex. NN, Col. 37, l. 15-30 (Sportsman Decl. ¶ 13.)

[10] The Caliper patent claims call this mixture a "first mixture".

[11] The Caliper patent claims call ATP a "second reagent" or a "phosphate donor group". ATP has three phosphates attached to it. The kinase will take one of the ATP phosphates and give it to the starting material.

[12] Claim 1 of the '774 patent calls this new mixture a "second mixture".

[13] Claim 1 of the '774 patent calls the product a "fluorescently labeled product having a substantially different charge than the first reagent" and the '141 patent calls it a "phosphorylated product."

When the reaction product binds to the "binding reagent", it will be slowed down allowing its fluorescent tag to emit light in one direction (high fluorescence polarization.) Scientists could then detect the high fluorescence polarization and know the kinase did its job, (and the drug did not work.) Conversely, if the kinase was inhibited and there was no reaction product created (no phosphate transferred by the kinase) there would be no binding with the binding reagent and only low fluorescence polarization.[15]

A publication by Seethala et al. ("Seethala") described exactly this fluorescence polarization method for assaying kinase activity, and did so before Nikiforov came up with his invention.

Barron Decl. ¶ 5, Ex. C). Seethala's binding reagent was an antibody.[16]

D. Caliper Failed to Disclose Material Prior Art (The Seethala Reference) to the U.S. Patent and Trademark Office

Seethala describes a kinase assay that uses fluorescence polarization in the same way that the Caliper method uses it. (Barron Decl. ¶¶ 5-7, 12, and 34.) It is therefore

[14] Claim 1 of the '774 patent calls the binding reagent a "polyionic polymer" and claim 1 of the '141 patent calls it a "polycationic component".

[15] Using the golf ball analogy, the starting material would be the golf ball with the glow-in-the-dark sticker. The reaction product would be the golf ball and sticker with an added phosphate group transferred by the activity of the kinase (if the kinase was not inhibited by the drug.) To slow down the reaction product and to make it distinguishable from any starting material, scientists would bind it to a large heavy molecule "the binding reagent"; like binding a large heavy medicine ball to the golf ball with sticker and added phosphate. This would slow the golf ball (reaction product) down and make it act more like the medicine ball, which would reduce the spin and tumble, and result in a more polarized light emission from glow-in-the-dark sticker.

[16] Seethala's antibody, like all antibodies, was a protein, and all proteins are polymers of amino acids. A "polymer" is made up of repeating units. Proteins are polymers made up of a chain of units called amino acids (which include tyrosine). Depending on the surrounding conditions, some of the amino acids in the antibody will have a positive electrical charge, some a negative charge, and others no charge. (Barron Decl. 5, Ex. C)

material prior art that was known to the inventor and to Caliper, and it should have been disclosed by them to the U.S. Patent and Trademark Office. It was not.

E.

The only change Dr. Nikiforov made to the Seethala fluorescence polarization method for kinase assays was to use a binding reagent that was not an antibody

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[20] Attached as Exhibit MM to the Miclean declaration.

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H. Caliper's Delay

On September 11, 2001, the '774 patent issued to Caliper. At this time, MDC had already released its first IMAP™ kit and was working to finalize production of its first IMAP™ kinase assay kits, which Caliper now accuses of infringing its '774 patent. (Sportsman Decl. ¶¶ 35-37, 41-42.) Caliper admits to knowing about MDC's work "in the fall of 2001." (Merion Supp. Decl. to Caliper's Mot. Prelim Inj. ¶ 16; Despite knowing about MDC's IMAP™ products (and even buying and testing three kits)[24] Caliper sent no "cease and desist" communications to MDC before filing suit, and delayed suing MDC for seven months after the '774 patent issued. Further, Caliper did not move for a preliminary injunction on the '774 patent at the time it filed the action in April of 2002. (Miclean Decl. Ex. S (Caliper's Complaint).)

The second Caliper patent, the '141 patent, which Caliper acknowledges "describes essentially the same method [as the '774 patent] in a slightly different way," (Caliper Br. at 15:24-25), issued October 29, 2002. While Caliper now tries to explain that the issuance of the '141 patent was delayed because of clerical errors in the patent office, the errors were actually Caliper's, and Caliper did nothing to follow up on the delay or mitigate it until after the application for the

[24] Caliper purchased a "PDE" IMAP™ kit in August 2001 and another in November 2001; Caliper purchased an SGK IMAP™ kit in February 2002. (Miclean Decl. Ex. KK, Ex. P; Nikiforov Tr. 72:22-76:22.)

'141 patent was abandoned. (See ft. 34, *infra*.) Once the '141 patent was issued in October 2002, Caliper amended its complaint to allege infringement, but, again, did not at that time move for a preliminary injunction on either patent. (Miclean Decl. Ex. T (Caliper's First Am. Complaint).) It was not until 16 months after Caliper's first patent issued, and the IMAP™ technology was disclosed by MDC to the world in September 2001, that Caliper brought this preliminary injunction motion.

I. Caliper Is Not Being Irreparably Harmed By Sales Of IMAP™ Assays

Caliper claims that its market position in high-throughput screening kinase assays is being irreparably harmed by MDC's sale of IMAP™ assays. (Caliper Br. at 3-4, 21-24.) This claim is without basis. Initially, Caliper does not offer a fluorescence polarization kinase assay kit (such as IMAP™) for sale. Instead, it sells a system that uses a mobility shift assay technique—not the fluorescence polarization technique of the patents-in-suit

Very recently, Caliper has begun to market KiSS™ (kinase selectivity screening), but this is a process, not a kinase assay kit. *compare with* Sportsman Decl. ¶¶ 42-44.) Thus, any claims or intimation that MDC has taken sales away from Caliper by selling the IMAP™ kinase assay kits are, at best, grossly overstated, and, at worst, false.

Further, Caliper has not used the technology described in the patents-in-suit in a commercial product, nor does it appear to have any plans to do so in the future. (Caliper Br. at 4, fn. 2;

Instead of standardized microplates, Caliper's methods use what they call a "LabChip"—a device having very small grooves, through which solutions are moved. (Oldfield Decl. ¶ 15; Miclean Decl. Ex. W.) Experiments on LabChips are read by special instruments that are marketed only by Caliper, and

Thus, even if

fluorescence polarization kinase assays could be done on LabChips, the results could not be seen using Caliper's LabChip equipment.

In addition, kinase assays are not the new, emerging field that Caliper makes them out to be. Well over ***half a billion*** kinase assays are done every year. (Oldfield Decl. ¶ 9, Ex. N; Sportsman Decl. ¶¶ 11-12.) As of November of 2000, nearly a year before the first of the patents-in-suit issued, there were at least ten companies offering twenty-eight different non-radioactive kinase assay kits. (Oldfield Decl. ¶ 10, Ex. O (The Scientist 14[22]:20, Nov. 13, 2000, and accompanying chart; Sportsman Decl. ¶ 23.) These long-available kits even include approaches that do not use antibodies, and do use fluorescent tags. *Id.* Currently, there are about twenty companies offering about thirty kinase assays, about a third of which are non-radioactive/non-antibody.

All of these many available kits are run on various existing high-throughput instruments. *Id.*

Caliper's claim of irreparable harm is based solely on the declaration of Michael Merion, plaintiff's Vice President of Sales. This declaration expounds on Dr. Merion's view of the kinase assay market and IMAP™'s supposed impact on Caliper's sales. But Dr. Merion's declaration is without foundation. In sharp contrast to both the statements and the implications in his declaration, in deposition Dr. Merion admitted:

Accordingly, Caliper's claims of irreparable harm should be viewed with much skepticism.

J. MDC Would Be Substantially Harmed By An Injunction

Caliper and MDC are both small, publicly traded companies. Caliper's motion for a preliminary injunction threatens to completely shut down MDC's IMAP™ business

The issuance of a preliminary injunction would place MDC at a great disadvantage both in the marketplace and in this litigation.

IV. ARGUMENT

A. A Preliminary Injunction Is A Harsh Remedy

As Caliper correctly observes, the law of the Federal Circuit governs the substantive standards underlying the grant or denial of preliminary injunctions in patent cases. *Hybritech, Inc. v. Abbott Labs*, 849 F.2d 1446, 1451 n.12 (Fed. Cir. 1988). The Federal Circuit on many occasions has cautioned that a preliminary injunction is a discretionary tool providing a drastic and extraordinary remedy that is not to be routinely granted. *See, e.g., Intel Corp. v. ULSI Sys. Tech.,*

Inc., 995 F.2d 1566, 1568 (Fed. Cir. 1993); *Ill. Tool Works, Inc. v. Grip-Pak, Inc.*, 906 F.2d 679, 683 (Fed. Cir. 1990) (citing 11 Charles A. Wright & Arthur R. Miller, Federal Practice and Procedure § 2948 (1969)). A party seeking a preliminary injunction must meet a well-established four-factor inquiry: (1) that it has a reasonable likelihood of success on the merits; (2) that it will suffer irreparable harm if preliminary relief is not granted; (3) that the balance of its hardships against the hardships of the party against whom the injunction is sought weighs in its favor; and (4) that the public interest is not adversely impacted. *Vehicular Techs. Corp. v. Titan Wheel Inc.*, 141 F.3d 1084, 1087-88 (Fed. Cir. 1998) and *Intel Corp. v. ULSI Sys. Technology*, 995 F.2d 1566 (1993).

The burden to show entitlement to a preliminary injunction is not light and rests always on the moving party. *Reebok Int'l Ltd. v. J. Baker, Inc.*, 32 F.3d 1552, 1555 (Fed. Cir. 1994)*8. Central to the movant's burden are the likelihood of success and the irreparable harm factors. *Sofamor Danek Group, Inc. v. DePuy-Motech, Inc.*, 74 F.3d 1216, 1219 (Fed. Cir. 1996). A movant in a patent infringement suit, must first show a reasonable likelihood of success on the merits that requires proof of both patent validity and infringement. *Id.* Specifically, "because of the extraordinary nature of the relief, the *patentee* carries the burden of showing likelihood of success on the merits with respect to the patent's validity, enforceability, and infringement." *Nutrition 21 v. United States*, 930 F.2d 867, 869 (Fed. Cir. 1991) (emphasis original). "In other words, if [the accused infringer] raises a 'substantial question' concerning validity, enforceability, or infringement (i.e., asserts a defense that [the patentee] cannot show 'lacks substantial merit') the preliminary injunction should not issue." *Genentech, Inc. v. Novo Nordisk*, 108 F.3d 1361, 1364 (Fed. Cir. 1997). Where there is no clear showing of a likelihood of success in proving infringement, there is no presumption of irreparable harm. *High Tech Med. Instrumentation, Inc. v. New Image Indus., Inc.*, 49 F.3d 1551, 1556 (Fed. Cir. 1995). In balancing the hardships, a weak showing of likelihood of success tips the balance in favor of the party against whom the injunction is sought. *Ill. Tool Works, supra*, 906 F.2d at 683.

B. Caliper Is Not Likely To Succeed At Trial

Caliper is not likely to succeed at trial, because the IMAP™ assays do not infringe the Caliper patent claims, and because those claims are invalid.

1. The IMAP™ assays do not infringe the '774 and '141 patents

In patent law, the scope of the protected invention is defined by the claims at the end of the patent. *Aro Mfg. Co. v. Convertible Top Replacement Co.*, 365 U.S. 336, 339 (1961) ("[T]he claims made in the patent are the sole measure of the grant . . . ."); *Johnson & Johnston Assocs. Inc. v. R.E. Serv. Co., Inc.*, 285 F.3d 1046, 1052 (Fed. Cir. 2002) ("Both the Supreme Court and this court have adhered to the fundamental principle that claims define the scope of patent protection."). Caliper has the burden of proving that the claims are infringed. *Novartis Corp. v. Ben Venue Labs., Inc.*, 271 F.3d 1043, 1046 (Fed. Cir. 2001). Whether or not a claim is infringed is determined in two steps: first, words and phrases in the claim are interpreted to determine the proper scope of the claim; second, the claim as interpreted is compared with the accused product or method to see if the product or method includes each and every element of the claims. *Telemac Cellular Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316, 1323 (Fed. Cir. 2001). Here, Claim 1 of the '774 and '141 patents, the only claims at issue in this motion, do not cover a product, they cover methods.[25] Thus, the IMAP™ assay kits sold by MDC cannot infringe the claims by themselves, contrary to Caliper's suggestions otherwise. (Caliper Br. at 1:1-11, 11:15-16.) Rather, the claims are only infringed if someone performs each and every step of the claimed methods using the IMAP™ assays. *EMI Group N. Am., Inc. v. Intel Corp.*, 157 F.3d 887, 896 (Fed. Cir. 1998).

a.

[25] Claim 1 of the '774 patent and claim 1 of the '141 patent are the only claims at issue in Caliper's motion. (Caliper Br., p. 12:5-10.) Moreover, Caliper only discusses literal infringement, and does not apply the doctrine of equivalents. Thus, this brief addresses only literal infringement of those two claims.

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[26] Miclean Decl. Ex. II [Caliper Prelim Claim Constructions], at p. 2:20-27 (construing "polyionic polymer" (the binding reagent) in claim 1 of the '774 patent), p. 9:3-11 (construing "polycationic component,"(the binding reagent in the '141 patent). For purposes of analyzing infringement, MDC has assumed that Caliper is correct in contending that the claims should be interpreted this way. However, MDC reserves the right to argue that they should not, and are therefore invalid under 35 U.S.C. § 112, as discussed below at ft. 30.

[27] Claims must be construed the same way for purposes of determining infringement as they are for determining validity. *See Amazon.com, Inc. v. BarnesandNoble.com, Inc.*, 239 F.3d 1343, 1351 (Fed. Cir. 2001).

b. IMAP™ assays do not include a "comparing" or "monitoring" step

Claim 1 of the '774 patent requires the step of "comparing a fluorescent polarization in the second mixture relative to the first mixture ...." (Miclean Decl. Ex. MM, Col. 29, Claim 1.)

This "comparing" step is, therefore, completely lacking from the instructions that accompany the IMAP™ assay kits. (Barron Decl. ¶¶ 29-30, 33.)

Claim 1 of the '141 patent requires the step of "monitoring a level of phosphorylated product produced by the activity of the kinase enzyme ...." (Miclean Decl. Ex. NN, Col. 37, l 25-30.) The concept of "monitoring" was added to the '141 patent application (the '774 patent does not use the term) to describe multiple measurements over time of the fluorescence polarization of a reaction mixture.[28] As already shown, the IMAP™ assays do not measure a ***difference*** in fluorescence polarization – nor do they make other multiple measurements of fluorescence polarization.

Although there are still more reasons why the IMAP™ assays do not infringe the claims of the '774 and '141 patents, for the sake of brevity those reasons are not presented here

c. Caliper has not shown that MDC uses IMAP™ assays to infring the patents, or induces or contributes to infringement by others

MDC cannot be held liable for infringement unless it performs the claimed methods itself (direct infringement), or unless it induces or contributes to infringement by others (indirect

[28] The term "monitoring" and related terms are first referenced in the '141 patent in Example 3, "***Time Course Monitoring*** of Enzyme Reactions by Fluorescence Polarization". (Miclean Decl. Ex. NN; '141 patent at Column 27:1-26 (emphasis added)). In that example, "assays were ***monitored over time*** in order to determine the efficacy of the fluorescence polarization detection methods of the present invention on ***monitoring reaction time courses***" (emphasis added). Example 4 explains that "[t]he fluorescent polarization detection methods of the present invention were also applied in ***monitoring the time course*** of a phosphatase assay." *Id.* at Column 27:27-45. In that example, "[t]he relative fluorescence polarization level was ***monitored over time*** for a control reaction (no enzyme) and a reaction mixture with different concentrations of phosphatase enzyme." *Id.* (emphasis added). As Example 7 explains, "[t]hermal denaturation experiments were also performed in the presence of polylysine, while ***monitoring fluorescence polarization changes*** in the reaction mixtures." ('141 patent at Column 29:44-46 (emphasis added)). ***In sum, the '141 patent consistently uses the term "monitoring" only to describe multiple fluorescence polarization measurements of the same sample.*** *See Bell Atl. Network Servs., Inc. v. Covad Communications Group, Inc.*, 262 F.3d 1258, 1268, 1270-71 (Fed. Cir. 2001) ("[S]pecification may define claim terms 'by implication,'" and "when a patentee uses a claim term throughout the entire patent specification, in a manner consistent with only a single meaning, he has defined that term 'by implication.'" The court found that the ordinary meaning of the disputed non-t chnical term "mode" was "sufficiently broad and amorphous that the scope of the claim language can be reconciled only with recourse to the written description.").

infringement). Even if it was possible to infringe the Caliper patent claims using the IMAP™ assays (which it is not), Caliper has failed to present sufficient evidence that MDC itself uses the IMAP™ assays in an infringing manner, or that MDC induces or contributes to such infringement by others.[29]

2. The Caliper patents are invalid and unenforceable

There also remains substantial questions concerning the validity and enforceability of the '774 and '141 patent claims in view of the prior art.[30] The only modification that Dr. Nikiforov's alleged invention makes to the prior art Seethala assay, is to use a non-antibody peptide as a binding reagent, instead of the antibody used in the Seethala assay. Indeed, Caliper does not dispute that every element of Claim 1 of the '774 and '141 patents, other than the particular binding reagent that they used, was disclosed in Seethala's prior art publication.[31] (See comparison diagrams attached as Ex. I to Barron Decl. ¶ 34.)

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[29] Caliper simply asserts, with no evidence, that MDC uses the IMAP™ assays to provide product demonstrations and support to customers. (Caliper Br. at 12:11-12). But Caliper has not established how MDC or anyone else has actually used the IMAP™ assays. Caliper has not met its burden of proving that MDC should be held liable because it contributed to or induced any infringement. A plaintiff asserting contributory infringement must prove four elements: (1) the defendant sold a component or material for use in practicing the patented method; (2) the component or material constitutes a material part of the invention; (3) the defendant knew that the item it sold was especially made or adapted for use in infringing the patented method; and (4) the item sold is not a staple article or commodity of commerce suitable for substantial noninfringing use. *See C.R. Bard, Inc. v. Advanced Cardiovascular Sys., Inc.*, 911 F.2d 670, 673 (Fed. Cir. 1990). In order to establish inducement of infringement, it must be shown that the alleged inducer knowingly and actively induced infringement. *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1363 (Fed. Cir. 2003). It must be established that the defendant possessed specific intent to encourage another's infringement and not merely that the defendant had knowledge of the acts alleged to constitute inducement. *Warner-Lambert*, 316 F.3d at 1363. The plaintiff has the burden of showing that the alleged infringer's actions induced infringing acts and that he knew or should have known his actions would induce actual infringements. *Id.; see also Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1468-69 (Fed. Cir. 1990) (discussing statutory development of the doctrine of active inducement of infringement). Caliper has not attempted to prove each and every one of these elements, and in particular has made no effort to show that the IMAP™ assays are not capable of substantial non-infringing uses or that MDC had the specific intent to encourage infringement by others.

[30] As discussed in Molecular Devices' Preliminary Invalidity Contentions, the claims of the '774 and '141 patents fail to meet several requirements of 35 U.S.C. § 112, in particular the written description requirement. (See Miclean Decl. Ex. X (MDC's Prelim Invalid. Cont. and Supp.).)

They are therefore invalid. *See Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479 (Fed. Cir. 1998) (finding claims invalid on written description grounds because the claims omitted "an essential element" of the invention disclosed in the original disclosure, and therefore impermissibly broadened the scope of the claims). For the sake of brevity, MDC's other invalidity arguments will not be discussed at greater length in this brief.

[31] Barron Decl. ¶ 34, Ex. I. There are many other publications that also disclose some or all of the elements of the claims, but for the sake of brevity those other references will not be discussed in this brief.

(every element of the claims. (Barron Decl. ¶ 34.) *See In re Paulsen*, 30 F.3d 1475, 1478-79 (Fed. Cir. 1994) ("A rejection for anticipation under section 102 requires that each and every limitation of the claimed invention be disclosed in a single prior art reference."). Indeed, the comparison diagrams of Exhibit I to the declaration of Barron, a slightly modified version of Exhibit E to Caliper's brief, shows how the prior art Seethala assay has each and every element of Caliper's claims thus anticipating (and invalidating) the Caliper patents.

Such non-disclosure of material prior art constitutes inequitable conduct sufficient to render the patents unenforceable.

[32] An antibody is a polymer of amino acids, with negative and positive charges as a result of those amino acids. (Miclean Decl. Ex. P; Nikiforov Tr. 159:15-160:1; 181:11-21.)

[33] Caliper's failure to disclose the Seethala publication is one basis for MDC'S position that the claims are unenforceable due to Caliper's inequitable conduct in failing to disclose material prior art to the United States Patent and Trademark Office ("the Patent Office"). (Miclean Decl. Ex. AA.) (*See also Elk Corp. of Dallas v. GAF Bldg. Materials Corp.*, 168 F.3d 28, 30 (Fed. Cir. 1999) (noting that a breach of patent applicants' duty to prosecute patent applications in the Patent Office "with candor, good faith, and honesty . . . may constitute inequitable conduct"); *LaBounty Mfg., Inc. v. U.S. Int'l Trade Comm'n*, 958 F.2d 1066, 1074, 1076 (Fed. Cir. 1992) (finding undisclosed prior art reference material for inequitable conduct analysis and noting that "[p]atent applicants are required to disclose to the examiner all information 'material to the examination of the application'"). For the sake of brevity, Caliper's inequitable conduct will not be discussed at greater length in this motion.

C. Caliper Will Not Be Irreparably Harmed In The Absence Of A Preliminary Injunction

Parties seeking pretrial injunctive relief must demonstrate they will be exposed to some irreparable harm if such relief is denied. *Vehicular Techs. Corp. v. Titan Wheel Int'l, Inc.*, 141 F.3d 1084, 1088 (Fed. Cir. 1998); *Associated Gen. Contractors of Cal. v. Coalition for Econ. Equity*, 950 F.2d 1401, 1410 (9th Cir. 1991). The threatened harm must be immediate and significant. *FMC Corp. v. United States*, 3 F.3d 424, 430 (Fed. Cir. 1993) (finding that plaintiff's failure to establish the extent of the irreparable harm precluded a grant of preliminary injunction); *Caribbean Marine Serv. Co. v. Baldrige*, 844 F.2d 668, 674 (9th Cir. 1988). To establish "irreparable injury", Caliper must demonstrate potential harm that cannot be redressed by a legal or equitable remedy following trial. The preliminary injunction must be the only way of protecting the plaintiff from such harm. *Campbell Soup Co. v. ConAgra, Inc.*, 977 F.2d 86, 91 (3d Cir. 1992). Caliper has not shown irreparable harm in the instant motion—its over year delay in seeking a preliminary injunction alone shows that the extraordinary relief of an injunction before a full trial on the merits is unwarranted.

1. Caliper Is Not Entitled To A Presumption Of Irreparable Harm

While a patentee may be entitled to a presumption of irreparable harm when it makes a strong showing of likelihood of success on the merits and a showing of continuing infringement, *see Reebok Int'l Ltd. v. J. Baker, Inc.*, 32 F.3d 1552, 1556 (Fed. Cir. 1994), there is no such presumption where, as here, there has been no strong showing of likelihood of success. S*ee Atari Corp. v. Sega of Am., Inc.*, 869 F. Supp. 783, 790 (N.D. Cal. 1994). MDC has demonstrated that Caliper is unlikely to succeed on the merits as to both infringement and validity. Caliper has not, therefore, established entitlement to a presumption of irreparable harm.

2. Caliper Unreasonably Delayed in Seeking Injunctive Relief

Caliper's claim of irreparable harm is belied by its over 16-month delay in seeking to enjoin MDC'S development and sale of IMAP™ assays. "[D]elay in seeking a remedy is an important factor bearing on the need for a preliminary injunction. *High Tech Med. Instrumentation, Inc.*, 49 F.3d at 1557; *see also Nutrition 21 v. United States*, 930 F.2d 867, 872 (Fed. Cir. 1991) (Patentee's

substantial delay before seeking a preliminary injunction "suggests that the status quo does not irreparably damage [the patentee]."); *T.J. Smith & Nephew Ltd.*, 821 F.2d 646, 648 (1987) (noting that presumption of irreparable harm would have been rebutted by a fifteen-month delay in seeking an injunction in combination with the grant of licenses).

Caliper has moved for a preliminary injunction a full sixteen months after its first patent issued and the MDC IMAP™ technology was disclosed to the world in September 2001. Caliper's motion simply comes too late. *Playboy Enters., Inc. v. Netscape Communications Corp.*, 55 F. Supp. 2d 1070, 1080, 1090 (C.D. Cal. 1999) (5-month delay after retaining the expert in filing preliminary injunction motion supported denial of motion); *Stokely-Van Camp, Inc. v. Coca-Cola Co.*, No. 86-C-6159, 1987 U.S. Dist. LEXIS 781, at *7 (N.D. Ill. Jan. 30, 1987) ("[T]he fact that [plaintiff] waited three months indicates a lack of a need for the extraordinary remedy of a preliminary injunction."); see also, *Programmed Tax Sys., Inc. v. Raytheon Co.*, 419 F. Supp. 1251, 1255 (S.D.N.Y. 1976).

Caliper has no excuse for its failure to file a preliminary injunction motion for 16 months after issuance of the '774 patent. To the extent Caliper claims the delay in filing its preliminary injunction motion was related to the delay in the issuance of the '141 patent, such argument is subterfuge. Initially, there is no reason Caliper could not have brought its motion based solely on the '774 patent, which, according to Caliper, is "essentially the same" as the '141 patent. (Caliper Br. at 15:24-26.) Further, delay in the issuance of the '141 patent was related to Caliper's inattention and neglect.[34] Caliper's claim that it had hoped to "prosecute this lawsuit in a

[34] Caliper argues that clerical errors in the patent office delayed the issuance of the '141 patent. (Caliper Br. at 20:9-13.) But it was Caliper, not the patent office, that was responsible for any delay. Caliper received a notice of the allowance of its claims on January 2, 2002, and paid its issuance fee on January 10, 2002. Then, on March 1, Caliper filed a continuation application in order to try and change the claims. But Caliper used the wrong procedure for the continuation and failed to withdraw the previous one. The new claims were allowed on March 8, 2002, but, because of Caliper's mistake, the fee that Caliper had already paid was never applied to the new application. More than five months later the PTO issued a notice of abandonment. Only then did Caliper act, explaining its mistakes and petitioning for the withdrawal of this holding. (Miclean Decl. Ex. BB (August 28, 2002 Pet. Withdraw Holding Aband.).) The petition was approved, and the patent eventually issued on October 29, 2002 – almost 8 full months after it was allowed. Caliper's procedural mistakes caused the delay, and that Caliper did not follow up on this delay can only be its own fault.

reasonable period of time without the need for a preliminary injunction proceeding" should also be viewed with skepticism where, as here, the case is being litigated within the normal time frame.[35]

Moreover, Caliper's veiled accusations that MDC has been delinquent in its discovery obligations, thus excusing Caliper's delay, are not only false, they are illogical. MDC's document production is substantially complete and it was completed in timely fashion (despite the fact that it was five times the size of Caliper's production.) (Miclean Decl. ¶ 14.) Fundamentally, though, MDC's discovery responses have nothing to do with Caliper's determination of the supposed harm that it is suffering.

3. Caliper's Licensing of the Patents-in-Suit Negates Any Claim Of Irreparable Harm

A patentee's willingness to license its patent to competitors shows that money is adequate compensation. *See High Tech Med. Instrumentation*, 49 F.3d at 1557; *see also Rosemount, Inc. v. ITC*, 910 F.2d 819, 821-22 (Fed. Cir. 1990); *T. J. Smith & Nephew*, 821 F.2d at 648. If money damages are sufficient, there is no irreparable harm because "any injury suffered by [the patentee] would be compensable in damages assessed as part of the final judgment in the case." *High Tech Med. Instrumentation*, 49 F.3d at 1557.

Contrary to the implication of Caliper's opening brief and the supporting Merion Decl. ¶ 14), Caliper ***does*** license its patents, including to Agilent

Indeed, it is Caliper's ***stated corporate policy*** to license its technology. For instance, in its corporate fact sheet, Caliper explains that it has two business models—direct sales and OEM business. (Miclean Decl. Ex. U, Corporate Summary, p. 1.) Caliper further explains that "[t]he OEM business provides chips and enabling technologies to vendors who then integrate the application solution and market it to their end customers. Caliper's partnership with Agilent Technologies, Inc. is a prime example of this latter approach." Id. That licensing is a focus of Caliper is supported by its public financial documents. In 2002, out of total revenues of less than

[35]The average time to trial in this district in 2002 was 23.5 months, even in non-patent cases. (Miclean Decl. Ex. CC (Judicial Caseload Profile, available on http://www.uscourts.gov/cgi-bin/cmsd2002.pl).) Even with the short, three-month delay caused by Caliper adding the '141 patent, this is consistent with the

$26M, over $9M are from license fees and contract revenue. (Miclean Decl. Ex. GG.) Caliper's willingness—indeed, desire—to license its technology indicates that money is sufficient to compensate it for the use of its technology. A preliminary injunction is therefore unwarranted.

4. Caliper Fails To Show How Its Reputation And Market Share Are Affected By MDC.

Caliper claims that its market position in high-throughput screening kinase assays is being harmed by MDC's alleged infringement. (Caliper Br. at 3-4, 21-24.) But, as discussed above, Caliper does not appear to currently offer a kinase assay kit (like IMAP™) for sale. Nor has Caliper used the technology described in the patents-in-suit in a commercial product,

Finally, kinase assays are a well-developed field with many competitors and technologies available. (Oldfield Decl. ¶¶ 9-10.)

Caliper offers no evidence that MDC'S IMAP™ products have had, or can have, any effect on Caliper's market share for kinase assays. Caliper has not identified any MDC customers that would purchase kinase assays from Caliper, as opposed to its many competitors, if the injunction issues. (See *infra*, p. 15, l. 8-28.) Also, MDC'S sales account for only about one percent of the total market for kinase assays. (Oldfield Decl. ¶ 9.)

Moreover, the fact that Caliper does not use the assay technology described in the patents-in-suit is a factor that weighs against a finding of irreparable harm. *Atari*, *supra*, 869 F. Supp. at 790-92. *See also Reiffin v. Microsoft Corp.*, 158 F. Supp. 2d 1016, 1028 (N.D. Cal. 2001) ("Given the fact that [the plaintiff] does not manufacture, sell or license any products based on his patents, he cannot point to any specific commercial interest that needs equitable protection.") (citing *High Tech Med. Instrumentation*, 49 F.3d at 1556 ("[T]he lack of commercial activity by the patentee is a significant factor in the calculus.").

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current trial date, which is 21 months after filing. Thus, Caliper knew, or at least should have known, the approximate time frame to trial that it could expect in this case.

The instruments and the assays made by MDC and other companies use standard microplates.[36] Because they are standardized, the instruments and the assays are cross-compatible. That is, you can use any assay on any microplate, and read it with almost any instrument. Industry data indicates that standard microplates make up the vast majority of all high-throughput screening. (Oldfield Decl. ¶ 13.) Caliper, however, has chosen to market a different, purportedly more "sophisticated" kind of plate and reader. Caliper's HTS systems have also been publicly criticized for use with enzymatic assays (like kinase enzyme assays) (Oldfield Decl. ¶¶ 13-15), and are slower and more expensive than other HTS systems. (Oldfield Decl. ¶ 15-16.) Caliper's failure in the marketplace has nothing to do with its patents or MDC, and everything to do with the risky choice to market something new that customers don't want. (Oldfield Decl. ¶¶ 13-16; Miclean Decl. Ex. PP.)

D. The Hardship That MDC Will Suffer If The Preliminary Injunction Is Granted Outweighs Any Potential Harm To Caliper

A preliminary injunction is a harsh remedy that here essentially gives Caliper its trial remedy before discovery has even been completed. Caliper's motion for a preliminary injunction threatens to completely shut down MDC'S IMAP™ business.

[36] Microplates are somewhat like a grid of tiny test wells attached together. These microplates come in multiple sizes that allow companies to do from 6-3456 experiments at the same time.

Injunctions are truly drastic remedies. They can often compel capitulation of a defendant regardless of the merits of its defense. While MDC vehemently disputes Caliper's infringement accusations and the validity of the patents-in-suit, an injunction may well make it prohibitive to litigate these issues. The hardship to MDC of an injunction outweighs any theoretical harm to Caliper caused by denial of its motion.

E. The Public Interest Dictates Against Granting Injunctive Relief

The scientists who use IMAP™ assays are doing important research on cancer, autoimmune diseases, inflammatory diseases (such as asthma), diabetes, and neurological and cardiovascular (heart) disorders. (Oldfield Decl. ¶ 8.) If a preliminary injunction issues, these researchers would be forced to switch assay approaches mid-stream.

Further, the legitimate public interest in competition and continuing critical research without interruption favors the denial of the motion for preliminary injunction. While there always exists a public interest in protecting the rights secured by a valid patent, the focus of the public interest analysis should be whether there exists some public interest that would be injured by the grant of the preliminary injunction. *Hybritech Inc. v. Abbott Labs.*, 849 F.2d 1446, 1458 (Fed. Cir. 1988); *see also Datascope Corp. v. Kontron Inc.*, 786 F.2d 398, 401 (Fed. Cir. 1986) (affirming district court's finding that public interest supported a denial of preliminary injunction because the accused infringer had "made some showing that the public will be harmed by an injunction"). The interest

in protection of patent rights can be counterbalanced by the interest in competition. *See Ill. Tool Works, Inc. v. Grip-Pak, Inc.*, 906 F.2d 679, 684 (Fed. Cir. 1990).

V. CONCLUSION

There is, therefore, no likelihood of success on the merits, and Caliper's motion for preliminary injunction should be denied.

Dated: April 1, 2003

FISH & RICHARDSON P.C.

By: _____
David J. Miclean

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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

CALIPER TECHNOLOGIES CORP.,

Plaintiff,

v.

MOLECULAR DEVICES CORPORATION,

Defendant.

AND RELATED COUNTERCLAIMS.

Case No. C 02-01837 JSW (JL)

DECLARATION OF ANDREW R. BARRON IN SUPPORT OF MOLECULAR DEVICES' OPPOSITION TO MOTION FOR PRELIMINARY INJUNCTION

[REDACTED VERSION]

Date: May 16, 2003
Time: 9:00 A.M.
Ctrm: 2

Judge: Honorable Jeffrey S. White

I, Andrew R. Barron, declare and state:

1. I have been retained by Fish & Richardson P.C. to offer my expert opinion concerning technical issues in this case. If called as a witness, I could competently testify to the following facts, all of which are based on my own personal knowledge and expertise.

My Expertise and Preparation

2. I am currently the Charles W. Duncan Jr. – Welch Chair of Chemistry and Professor of Materials Science at Rice University, Houston, TX.

3. I am an expert in chemistry and materials science, with particular experience in the area of the Group 13 elements including gallium. I have been performing independent research in this area for approximately seventeen years. My particular expertise with respect to the case includes extensive experience with the reaction and structural characterization of gallium compounds, especially the reactions with phosphate and related compounds. Evidence of this expertise is the receipt of two awards from the Royal Society of Chemistry, the first being the Meldola Medal and Prize in 1990, and in 1995, I was awarded the Corday Morgan Medal and Prize, both for my research of gallium chemistry. I have published over 250 peer-reviewed papers, 5 book chapters, and am a named inventor in approximately 12 patents. I have published a number of papers directly relating to gallium phosphate chemistry. I have consulted for a number of US and foreign companies in the area of gallium chemistry. Further references, a publication list, and related documents are given in my *curriculum vitae*, see attached Exhibit A.

4. In considering the aspects of this case and formulating my opinions expressed herein, I have used my knowledge and expertise of chemistry. In addition, I have used my knowledge gained over years of studying general scientific texts and specialist journal articles, attending scientific conferences, and engaging in scholarly discussions with colleagues. In particular in this case, I have reviewed a number of papers, discovery documents, deposition transcripts, patents, and I have had discussions with MDC personnel. I have relied on specific documents that are referenced throughout this text. A complete list of the materials I have reviewed in preparing this declaration is attached as Exhibit B. My work is continuing, however, and I may supplement this declaration if additional information is produced by Caliper and provided to me. Further, my testimony may contain additional information that I receive or gain between now and that time. At the hearing, if called to testify, I expect to use demonstrative exhibits, including any Figures from my report, but I have not yet decided on them specifically.

Previously Known Kinase Assay Methods Using Fluorescence Polarization

5. Caliper wasn't the first to use fluorescence polarization in a kinase assay. Kinase assays have been accomplished previously using fluorescence polarization, as described in a publication by

Seethala and Menzel, "A Homogenous, Fluorescence Polarization Assay for Src-Family Tyrosine Kinases," *Analytical Biochemistry*, **253**, 210-218 (1997), attached as Exhibit C ("Seethala").

6. Seethala described the use of an antibody as a binding reagent to affect the fluorescence polarization of phosphotyrosine. The phophotyrosine was the product of a kinase reaction. The phosphotyrosine is equivalent to the phosphoserine disclosed in Examples 1 and 2 in Caliper's U.S. Patent No., 6,287,774 ("the '774 patent"), col. 23, line 60 to col. 24, line 67, and Examples 1-3 in Caliper's U.S. Patent No. 6,472,141 ("the '141 patent"), col. 25, line 26 to col. 27, line 26.

7. As described in a later publication by Wilkinson, "Tyr'd and True: Immunochemical reagents and kits for studying tyrosine phosphorylation," *The Scientist*, **13**[10]:21 (May 10, 1999), a copy of which is attached as Exhibit D ("Wilkinson"), the interaction between the antibodies used by Seethala and the phosphotyrosine involves electrostatic interactions. Wilkinson details the antibodies used in his study. These include antibodies designated as PY20, PY54, and PY69 (Wilkinson at MDC 0009057). Seethala uses these same antibodies in his study (Seethala at MDC 0009043).

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The IMAP Assay Only Measures the Fluorescence Polarization of a Mixture Once

29. The product inserts that accompany the IMAP assay kits, on which Caliper relies, do not instruct users to perform either a "comparing" step or a "monitoring" step. Langer Ex. C. Instead, they instruct users to make only one measurement of fluorescence polarization for a given sample, after the reaction has been incubated to permit it to finish. *Id.* at MDC 0024903 (steps 9-10).

30. In the IMAP assay, only the fluorescent polarization of the second mixture is measured – no measurement is made of a first mixture before ATP is added to it, so there is no "before and after" comparison made. Langer Ex. C at MDC 0024902-03 (steps 1-11). A comparison step is, therefore, completely lacking from the instructions that accompany the IMAP assay kits.

31. Moreover, the IMAP assay instructions do not tell users to monitor the reaction – they do not tell users to make multiple measurements of the fluorescence polarization of a reaction mixture. The IMAP assays do not measure a ***difference*** in fluorescence polarization – nor do they

fluo

make other multiple measurements of fluorescence polarization. Instead, they only measure the fluorescence polarization once, at the very end, after the reaction has been allowed to complete. Langer Ex. C at MDC 0024903 (steps 9-10).

Conclusions

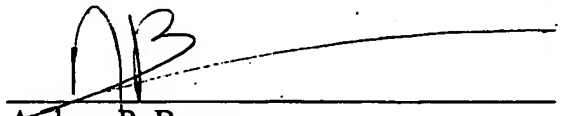
32. If the Caliper patent claims – claim 1 of the '774 patent and claim 1 of the '141 patent -- require charge-dependent, non-specific interactions, then it is my opinion that they are not infringed by the use of the IMAP assay, because the IMAP assay does not use charge-dependent, non-specific interactions. Instead, the IMAP assay uses coordinate covalent binding. This is illustrated with the figures in Exhibit I.

33. Moreover, if the Caliper patent claims require making more than one measurement of the fluorescence polarization of a mixture, then it is my opinion that users who follow the instructions that accompany the IMAP assay kits do not infringe the claims, because those instructions only tell users to make one single measurement of the fluorescence polarization of a given mixture.

34. In addition, every element of claims 1 of the '774 and '141 patents is present in the Seethala method. I understand that Seethala is prior art, and that if every element of claims is present in a prior art reference, the claims are invalid, and thus I conclude claims 1 of the '774 and '141 patents are invalid. This is illustrated with the figures in Exhibit I.

35. I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct to the best of my knowledge.

Executed this 30 day of March, 2003 at Houston, Texas.



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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

CALIPER TECHNOLOGIES CORP.,

Plaintiff,

v.

MOLECULAR DEVICES CORPORATION,

Defendant.

AND RELATED COUNTERCLAIMS.

Case No. C 02-01837 JSW (JL)

DECLARATION OF J. RICHARD SPORTSMAN IN SUPPORT OF MOLECULAR DEVICES'S OPPOSITION TO CALIPER TECHNOLOGIES' MOTION FOR PRELIMINARY INJUNCTION

[REDACTED VERSION]

Date: May 16, 2003
Time: 9:00 A.M.
Ctrm: 2

Judge: Honorable Jeffrey S. White

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David J. Miclean (# 115098)
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Date: May 16, 2003
Time: 9:00 A.M.
Ctrm: 2

Judge: Honorable Jeffrey S. White

I, J. Richard Sportsman, declare and state:

1. I am currently an employee of defendant/counterclaimant Molecular Devices Corporation ("MDC"), with the position of Vice President, Assay and Reagent Research and Development. If called as a witness, I could competently testify to the following facts, all of which are within my own personal knowledge.

General Background

2. I am trained as an analytical biochemist. I received a Ph.D. in Analytical Chemistry from the University of Arizona in 1982, and I completed post-doctoral studies in Clinical Immunology at Scripps Clinic and Research Foundation in 1984.

3. I have worked at several biotechnology or pharmaceutical companies, including Eli Lilly and Company, SyStemix, Inc., and Terrapin Technologies (now Telik). Each of these companies is or was involved in drug discovery or development of human therapeutics. In my work at these companies, I have acquired special expertise in methods of drug discovery using immunological techniques and fluorescence polarization.

4. I have been employed by MDC or LJL Biosystems ("LJL") since August 1998. In August 1998, I joined LJL, which merged with MDC two years later in August 2000. At LJL and MDC, I have been responsible for research on various chemical tests ("assays") and the development of kits that use such tests.

5. Further details of my employment history and qualifications are described in my resume, which is attached as Ex. K of this Declaration.

Background for Our Work in Drug Discovery Using Fluorescence Polarization

6. In 1993, I began employment at Terrapin Technologies (now and hereafter Telik) as Director of Molecular Recognition. My research group at Telik was working to develop drug discovery methods suitable for high throughput screening of potential drug compounds. "High throughput screening" or "HTS" is a strategy for drug discovery that came of age in the mid to late 1990s. It uses cutting-edge technology, including highly automated laboratory machines, to simultaneously test large numbers of samples – i.e. drug candidates – for potentially desirable characteristics. By screening many samples, we improve our chances of finding new and useful drugs.

7. At Telik, we were working to develop drug discovery methods that use a detection technique called "fluorescence polarization." Fluorescence is similar to what makes glow-in-the-dark toys and posters visible after you shine light on them. Things that fluoresce emit light shortly after being "hit" with light. Scientists can attach a molecule that emits fluorescent light – known as

a "fluorescent tag" – to a molecule that does not emit fluorescent light, and which would otherwise be invisible. Scientists can then detect the otherwise invisible molecule by the fluorescent "glow" of the tag that was attached to it.

8. With the fluorescence polarization technique, scientists measure the polarization of the light that is emitted by the fluorescent tag on a molecule. All light has a polarization direction; it is as fundamental as color. Much like a light beam can be white (mixed colors) or one color, a light beam can have low polarization (many polarization directions) or high polarization (one polarization direction). Natural light, like sunlight, has a low polarization and polarized light, like that which passes through polarized glasses, has a high polarization. When a fluorescent molecule absorbs light with high polarization it naturally emits polarized light. If a fluorescent molecule is stationary for the time between absorbing light and emitting it, one can observe the highly polarized emission. However molecules in solution spin and tumble about. Small molecules tumble quickly. Large ones move more slowly. A group of small, quickly tumbling fluorescent molecules will emit light polarized in many random directions. The net result is light with low polarization. Conversely, a group of large, slowly moving fluorescent molecules tends to emit light with a high polarization.

9. The fluorescence polarization of molecules can be used to determine whether there are large or small fluorescent molecules in a sample or mixture: Small fluorescent molecules will have low polarization, while large ones will have high polarization.

10. Fluorescence polarization also can be used to determine whether a small fluorescently tagged molecule is bound to a bigger molecule. When the small molecule is bound to a large molecule, it "acts and looks" like a large molecule. That is, it tumbles slowly and has a high polarization. If the small molecule does not bind to the large one, it acts and looks like the small molecule that it is, tumbling fast and having a low polarization. Thus, measuring the fluorescence polarization is one way to determine whether the small molecule is of a kind that could bind to a particular large one. *Low* polarization indicates that the small molecule did *not* bind; *high* polarization indicates that the small molecule *did* bind to the larger one.

11. Fluorescence polarization has been known since the 1920s, when scientists first developed the techniques to measure and analyze it. In the 1960s, scientists began using

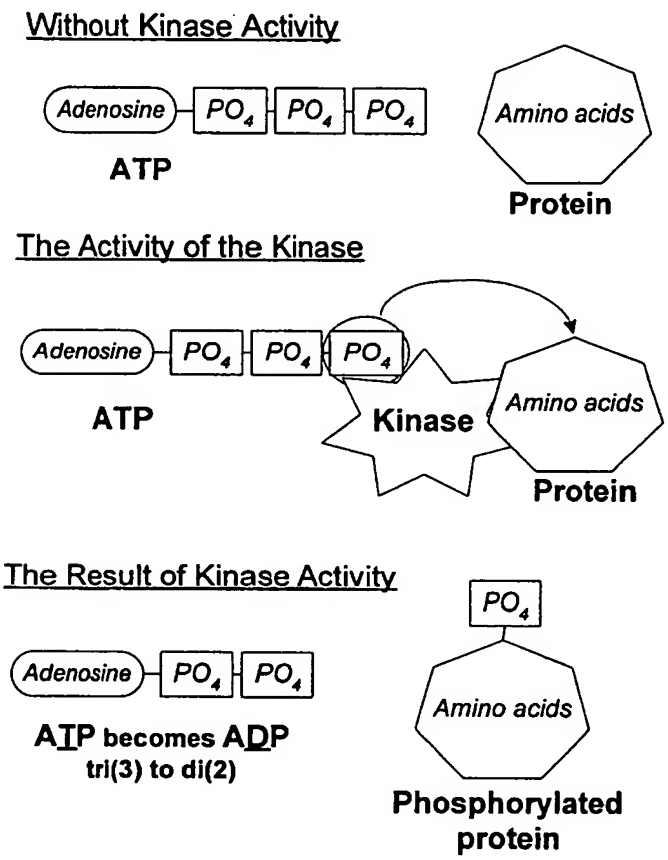
fluorescence polarization to detect the binding of molecules as described above. Beginning in the 1980s, fluorescence polarization was used to detect binding in many immunological studies. In the early to mid 1990s, machines were developed that allowed fluorescence polarization to be used for high throughput screening in drug discovery, so that numerous samples could be easily evaluated at the same time.

Background For Our Work on Kinases

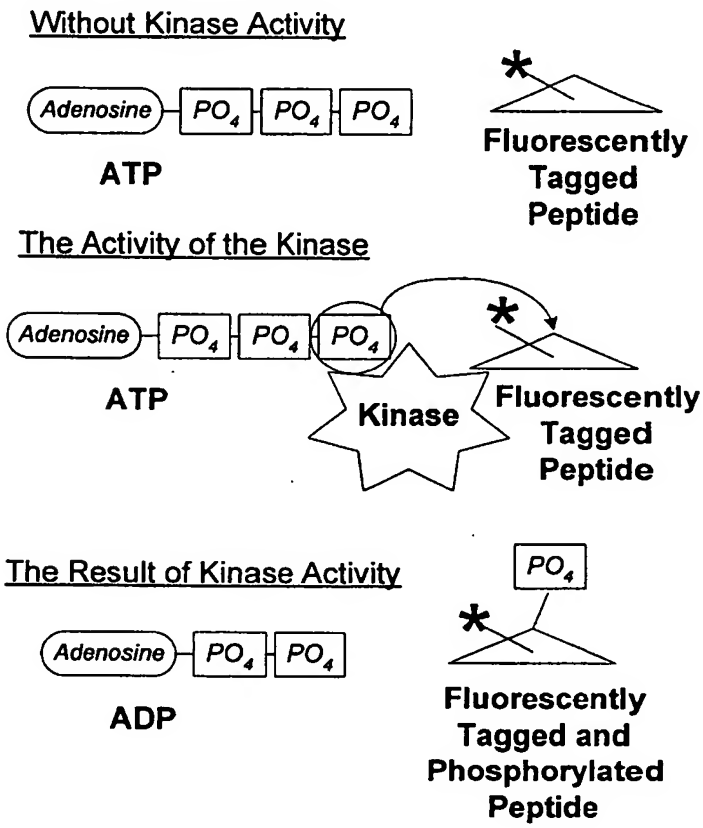
12. From 1993 to 1998, while I was at Telik, I and some colleagues were looking for a method that could be used in high throughput screening of chemicals that might affect kinase enzyme activity. Kinases are enzymes that occur naturally in the body, and they are essential for the normal function of cells in our bodies. For example, kinases are important for communication among cells, and their activity can affect cell growth and survival. Abnormal kinase activity may be partly responsible for some cancers, autoimmune diseases, inflammatory diseases (such as asthma), diabetes, neurological disorders and cardiovascular (heart) diseases. Thus, there is considerable interest in finding drugs that inhibit kinase activity ("kinase inhibitors"), and which could therefore be used to control these diseases.

13. Although there are many different kinase enzymes in the body, each kinase does one simple thing. It transfers or "moves" a special chemical group called a phosphate (symbolized as PO_4 because it has one phosphorous atom and four oxygen atoms) from one molecule to another. The kinase removes the phosphate from a molecule such as ATP – which stands for adenosine *tri*phosphate. As its names suggests, ATP is a molecule that has *three* phosphates. The kinase removes one of ATP's phosphates, and attaches that phosphate to another molecule, which could be one of many different proteins. (The removal of a phosphate from ATP transforms it into ADP, which stands for adenosine *di*phosphate; as its name indicates, ADP has *two* phosphates instead of three, since one phosphate was taken away by the kinase enzyme.) The process of the kinase transferring a phosphate to a protein is called "phosphorylation," and the molecule receiving the phosphate is then considered "phosphorylated."

14. Here is a diagram that shows what kinases do:



15. In laboratory studies of kinase activity, a "peptide" is typically used instead of a full-length protein. A peptide is just a small piece of a protein. The peptide can be fluorescently tagged, as shown here:



16. There are two kinds of kinases: "tyrosine kinases" and "serine/threonine kinases." They differ in terms of where on the protein or peptide the phosphate is attached. Tyrosine kinases attach a phosphate group to a "tyrosine" (one of the 20 amino acids that make up all proteins and peptides), turning it into a "phosphotyrosine." Serine/Threonine kinases attach a phosphate group to either a "serine" or a "threonine" (two other of the 20 amino acids). Thus, there are two kinds of phosphorylated proteins or peptide: those that have a phosphotyrosine, and those that have a phosphoserine or a phosphothreonine.

Development of our Fluorescence Polarization Antibody Method to Test Tyrosine Kinases

17. While at Telik, from 1993 to 1998, I and my colleagues developed what has been called a "direct" method to screen for chemicals or compounds that inhibit tyrosine kinase activity. The method used fluorescence polarization and antibodies.

18. Antibodies are a special kind of molecule produced by the immune systems of humans and animals. An antibody binds to some specific part of some other molecule. For example, an antibody can bind only to a specific region of a protein. We used an antibody that would bind to a single amino acid in a protein – namely, tyrosine. However, our antibody would bind to tyrosine *only if* that tyrosine had been phosphorylated by a tyrosine kinase (i.e. only if the tyrosine has a phosphate attached to it).

19. We used this "phosphotyrosine antibody" and fluorescence polarization to determine whether or not a phosphate had been transferred by a kinase to a peptide. If a phosphate had been transferred by the kinase, the antibody would bind to the phosphorylated peptide, which would then "act and look" like a larger molecule. That is, it would tumble slowly and have a high polarization. If the kinase enzyme was inhibited, and the peptide was not phosphorylated, the peptide would act and look like the small molecule that it is, tumbling fast and having a low polarization.

20. Because antibodies are expensive, we also devised a variation on this fluorescence polarization assay method, called a "competition" method, that requires fewer antibodies and is therefore less expensive than the "direct" method described above. We filed a patent application on our fluorescence polarization / antibody methods for testing kinase activity. The patent rights were assigned to Telik.

21. The direct method that we devised at Telik is similar to the fluorescence polarization kinase assay methods described by R. Seethala and R. Menzel in their 1997 paper entitled A Homogenous, Fluorescence Polarization Assay for Src-Family Tyrosine Kinases. A true and correct copy is attached hereto as Ex. L. All of these methods use an antibody to bind to a phosphorylated peptide or protein so that it can be detected by a measurement of fluorescence polarization.

22. The Analyst is a large, automated instrument for doing high-throughput screening. It can measure

different types of physical features of a sample. One of the things that it can measure is fluorescence polarization. The Analyst can also measure fluorescence intensity, time-resolved fluorescence, luminescence, and absorbance. We used the Analyst to monitor fluorescence polarization in the competition methods noted above. It worked well.

23.

LJL released the first such kit, the "TKX" kit, in April 1998. This and similar kits have been sold by MDC since the LJL – MDC merger in August 2000.

The Next Step: Our Invention of IMAP™

24. Fluorescence polarization methods that use proteins such as antibodies to monitor kinase activity have a number of undesirable features. First, antibody binding is a complicated interaction, involving both structural matching of the protein and the antibody, and various types of interactions including electrostatic interactions. Many things can interfere with the binding, including, for example, the acidity and the salt content of a solution. Second, the competition methods have a relatively weak fluorescent signal, so measuring the fluorescence polarization is difficult. If mistakes are too common, the results are simply not meaningful. Third, there are no antibodies that bind generically to phosphoserine or phosphothreonine (regardless of the protein or peptide), so the methods cannot be readily commercialized for use with all serine/threonine kinases – only for tyrosine kinases. Lastly, antibodies are proteins and, like any protein, their structure and function can be completely disrupted by certain conditions, such as heat or acidity, making them difficult to handle and use.

25. When I joined LJL in August 1998, I was interested in developing assay methods that could be used to test all kinases (not just the tyrosine kinases), and which would be robust and easy to use.

26. I knew about the specific nature of bonding between phosphate and iron (Fe(III)) for at least two reasons. First, phosphate was commonly used to determine the presence of iron in a solution; it would bind specifically to the iron, and the bound complexes could be detected in various ways. Second, work published in the 1980's by Porath and others described the use of beads coated with iron to bind specifically to phosphorylated peptides and proteins.

The work described by Porath is a type of Immobilized Metal Affinity Chromatography – "IMAC" for short. Chromatography is a common laboratory technique. It uses a column packed full of beads. A solution is poured over the beads in the column, and certain components of the solution bind to the beads while others flow through the column. In this way, the components that bind to the beads can be separated from those that do not.

I then read an article by M. Posewitz and P. Tempst entitled Immobilized Gallium (III) Affinity Chromatography of Phosphopeptides. A true and correct copy is attached hereto as Ex. M. This article shows quite clearly that the metal called gallium (Ga(III)) works better than iron in IMAC of phosphorylated proteins and peptides.

Commercial Development of IMAP™

38. We later decided to call our methodology "IMAP™" as a play on "IMAC" – the affinity chromatography technology that had inspired it. IMAC stands for "immobilized metal affinity column," while IMAP™ is sometimes said to stand for "immobilized metal affinity for phosphate."

40.

41. I gave a presentation about our IMAP™ technology at the Society for Biomolecular Screening conference in Baltimore, Maryland, September 10-13, 2001. Theo Nikiforov and other Caliper employees were present at the conference and attended my presentation.

42. Aside from the PDE kit, MDC's first two IMAP™ kits were released in December of 2001. To date, MDC has developed 17 types of kits (other than the PDE kit) that rely on the IMAP™ technology. Two types were released in December 2001 (Akt and SGK), two in March 2002 (p38 and MAPKAP-K2), six in June 2002 (fyn, lck, src, PRAK, MSK1, PP2A), and seven in December 2002 (Blk, Lyn, Syk, CHK1, CHk2, ROCKII, and PTP-1B). The kits are identical except for the particular enzyme and substrate that each contains. Each type of kit is named for the particular enzyme that it contains. Most of the kits include kinase. Two kits, PTP-1B and PP2A, contain a type of enzyme called a phosphatase. A phosphatase *removes* a phosphate from a peptide

or protein (in contrast to a kinase, which *add*s a phosphate to a peptide or protein). Because the enzyme and peptide are included, each kit is "ready-to-use."

43. Each IMAP™ kit is available in "explorer" size (enough material for 800 tests) and "bulk" size (enough material for 8,000 tests). Each IMAP™ kit contains the enzyme (i.e. a particular kinase or phosphatase, or PDE), a fluorescently tagged substrate (e.g. a peptide upon which the enzyme can act), and a solution or "buffer" for mixing them. Each kit also contains gallium-coated nanoparticles (the "binding reagent") and a special solution (the "binding buffer"), which are combined by the user just before use (to make the "binding solution"). ATP must be supplied by the user.

44. MDC sells its binding buffer and binding reagent in bulk, without enzymes or peptides, under the Screening Express program and the IMAP™ purchase plan. These programs allow companies who are able to develop their own particular combinations of enzymes and peptides to purchase only the binding reagent that they need in order to use the IMAP™ technology.

45. IMAP™ kinase kits (or materials purchased under the "IMAP™ purchase plan" or "screening express" products) are used to screen potential drug candidates as follows. All of these steps happen in each little well of a multi-well (e.g. a 384- or 1536-well) microplate:

a. First, the kinase and any drug compounds being tested (i.e. as potential inhibitors of the kinase) are mixed together in a well and incubated. The ensuing test will determine whether the drug inhibits the normal function of the kinase, which is to transfer a phosphate from ATP to a peptide, making it a phosphorylated peptide (see diagrams at Paragraphs 14 and 15).

b. Next, ATP and fluorescently tagged peptide are added to the well and incubated. If the kinase is not inhibited by the drug compound being tested, it will transfer phosphate from the ATP to the fluorescently tagged peptide, making phosphorylated and fluorescently tagged peptide. This phosphorylated peptide will still be small molecules that tumble quickly and emit light with low fluorescence polarization. Thus, the initial un-phosphorylated fluorescently tagged peptide (if there is any left)

and phosphorylated fluorescently tagged peptide are indistinguishable by fluorescent polarization.

c. To determine if the fluorescently tagged peptide was phosphorylated by the kinase in step b (and therefore whether the kinase was inhibited or not), a gallium-coated nanoparticle is mixed in a binding solution and added to the well. The binding solution stops the kinase reaction.

the larger gallium-coated nanoparticle will bind to the phosphorylated peptide (that is, it will bind to the phosphate on that peptide). It will not bind to the fluorescently tagged peptide if the kinase was inhibited and not able to "phosphorylate" the peptide. The purpose of binding the phosphorylated peptide to the gallium-coated nanoparticle is to make a small molecule (the fluorescently tagged peptide), having low fluorescence polarization, into a bigger molecule, having high fluorescence polarization.

d. The last step is to measure the fluorescence polarization of the chemical mixture in the well. If the kinase did its job and transferred the phosphate from the ATP to the peptide (making it into a phosphorylated peptide), the phosphorylated peptide will bind specifically and robustly, with a coordinate covalent bond, to the larger gallium-coated nanoparticle. The binding will create a larger molecule having high fluorescence polarization. The high fluorescence polarization tells the scientist that the drug did *not* work – the kinase was not inhibited. Conversely, if the drug worked and the kinase was inhibited, such that the peptide was not phosphorylated, then the fluorescently tagged peptide will not bind to the gallium-coated nanoparticle. It will remain a mere fluorescently tagged peptide, tumbling quickly and having low fluorescent polarization..

Summary

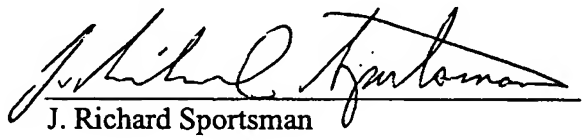
46.

I developed IMAP™ with others at MDC based on the available literature, our ideas, and our

experiments, and did so well prior to the public issuance of the patents at issue in this case, U.S. Patent Nos. 6,287,774 and 6,472,141 (the '774 and '141 patents). Neither I nor any other scientists at MDC copied or used the system of the '141 and '774 patents in devising our IMAP™ system.

47. I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct to the best of my knowledge.

Executed this 31st day of March, 2003 at Sunnyvale, California.



J. Richard Sportsman